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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/662,454	09/14/2000	Masayuki Yanagi	2026-4276US1	9114

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William S. Feiler, Esq.
Morgan & Finnegan, LLP
345 Park Avenue
New York, NY 10154

EXAMINER

LEFFERS JR, GERALD G

ART UNIT	PAPER NUMBER
1636	9

DATE MAILED: 11/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/662,454	YANAGI, ET AL.
	Examiner	Art Unit
	Gerald G Leffers Jr.	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 09 September 2002.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 42,43,45-53 and 55-57 is/are pending in the application.

4a) Of the above claim(s) 46,47,49 and 50 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 42-43, 45, 48, 51-53, 55-57 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.

4) Interview Summary (PTO-413) Paper No(s). _____.

5) Notice of Informal Patent Application (PTO-152)

6) Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 9/9/02 as Paper No. 8, in which several claims were amended (claims 42-43, 45, 48, 51-53 and 55-57) and in which claims were cancelled (claims 44 and 54). Claims 42-43, 45-53, 55-57 are pending in this application, with claims 46-47, 49-50 withdrawn from consideration as being directed to nonelected inventions.

Any rejection of record in the previous office action, Paper No. 6 mailed 4/9/02, that is not addressed in this action has been withdrawn. This action is FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-43, 45, 48, 51-53 and 55-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record in Paper No. 6, mailed 4/9/02 and repeated below. The rejection was originally made against claims 43, 55-57 and is hereby extended to amended claims 42, 45, 48 and 51-53.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of

experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: Each of the rejected claims is drawn towards methods of immunizing an animal against hepatitis C virus (HCV) by utilizing a nucleic acid composition wherein the nucleic acid encodes a hepatitis C virus and wherein expression of the nucleic acid in transfected cells results in production of virus. The claimed invention is thus exceedingly complex, involving the administration of a nucleic acid in order to elicit a protective or therapeutic immune response to the polypeptide(s) encoded by the nucleic acid.

Breadth of the claims: The breadth of the claims only exacerbates the complexity of the invention. The claimed methods are to be practiced on any animal, including humans, regardless if whether the animal is susceptible to HCV infection or not. Additionally, the nucleic acid composition is to be effective in producing a therapeutic or protective response in animals already infected with HCV, or in animals which have yet to be exposed to HCV. Moreover, the limitation that the nucleic acid of the composition be able to produce virus upon transfection in a cell means that there is the possibility of productive infection of the virus resulting in, or worsening, HCV infection of the treated animal.

Guidance of the specification: The specification provides little actual guidance with regard to practicing the claimed invention other than providing lists of pharmaceutical carriers and routes of administration, etc. Little guidance is given, for example, to the type of DNA construct that would be required in order to drive expression of the nucleic acid in order to efficiently produce virus in an infected host such that a protective or therapeutic immune response is induced. Little guidance is provided as to how one could construct a nucleic acid

encoding a productive HCV (i.e. a nucleic acid whose expression results in the production of virus by transfected cells) yet which is attenuated such that the pathologies associated with hepatitis infection are not produced. The specification merely indicates that attenuated viruses can be achieved by serial passage on appropriate cell lines. No guidance is given with regard to modification of specific regions of HCV that would result in such an attenuated virus.

The existence of working examples: The working examples are solely directed towards demonstrating that at least some full-length clones of HCV can be productive if introduced directly into the liver of chimpanzees. Not all of the exemplified full-length clones are infective in vivo. Indeed, even within the complex “quasi-species” of HCV clones obtained from infected animals, not all of the nucleic acids obtained from a single animal are infective. It is not at all clear from the working examples that one can necessarily predict which clones will produce virus upon transfection and which ones will not. No other means of introducing nucleic acids into the cells of an animal, other than by direct injection into the liver, are exemplified in the specification.

State of the art: At the time of filing for the instant application there appear to have been no known vaccines effective for the treatment of animals infected by HCV or effective in the prophylactic protection against HCV infection. At the time of filing for the instant application there appears to be little guidance with regard to the productive transfection of cells in vivo with nucleic acids encoding HCV such that an attenuated virus that does not cause pathology is produced. Indeed, at the time of filing the level of understanding the pathogenesis of hepatitis C was underdeveloped. The prior art teaches, “Despite great progress in understanding the natural history of the disease, fundamental aspects of the pathogenesis of hepatitis C remain unknown.”

(Nelson Fausto, American Journal of Pathology, August 1997, Vol. 151, No. 2, page 361, first column). The only animal model system for studying HCV infection is the chimpanzee. It is unclear from the prior art how closely HCV infection in the chimpanzee follows the events of human HCV infection. Also, it is unclear how closely results seen for the generation of a protective or therapeutic immune response against HCV in chimpanzees in response to transfection with a nucleic acid composition will carry over to humans.

Predictability of the art: Given that an effective vaccine, much less a nucleic acid-based vaccine, has yet to be produced against HCV; given that the prior art and specification do not make clear what specific changes can be made to produce a nucleic acid whose expression will result in an attenuated virus; and given that it is not at all clear that results seen in the chimpanzee model system will necessarily carry over to humans, it would be unpredictable before hand as to whether a particular nucleic acid construct will function in vivo to produce an attenuated virus as well as producing a protective or therapeutic immune response.

The amount of experimentation necessary: Given the whole of the factors discussed above, it would've required undue, unpredictable experimentation for one of skill in the art to practice the claimed invention at the time of filing. If one of skill in the art wanted to practice the claimed method with humans, for example, one of skill in the art would have to first envision a particular nucleic acid sequence encoding an HCV virus, envision an appropriate construct to drive expression of the nucleic acid sequence in target tissue such that attenuated viruses are produced upon transfection and construct the particular nucleic acid sequence/construct. One would then have to test the construct for its ability to produce viruses upon transfection of target cells (e.g. in chimpanzees). If unsuccessful, which is likely given the lack of guidance provided

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by the specification and prior art as to which nucleic acids will cause production of viruses upon transfection into host cells and based upon applicants' own results that indicate that even within the "quasi-species" of clones isolated from a single animal not all clones are infective, one would then have to either envision a modification of the first construct/means of delivery/dose, etc., or envision an entirely new combination of nucleic acid construct/means of delivery/dose and test the modified or new combination of nucleic acid construct/means of delivery/dose to determine if virus is produced following transfection *in vivo*. If unsuccessful, which is likely given the lack of guidance provided by the specification and prior art as to which nucleic acids will cause production of viruses upon transfection into host cells and based upon applicants' own results that indicate that even within the "quasi-species" of clones isolated from a single animal not all clones are infective, the skilled artisan would have to repeat the entire unpredictable process until a combination of nucleic acid construct/delivery means/dose is identified.

Once a combination of nucleic acid construct/delivery means/dose is identified as producing virus upon transfection *in vivo*, it will be necessary to determine the pathological effects of virus production on the animal model (i.e. in chimpanzees). If the nucleic acid construct does not encode an attenuated virus with regard to the pathologies associated with HCV infection, which is likely given the lack of guidance in the prior art or specification as to how one would actually construct a nucleic acid encoding an attenuated HCV virus and given the underdeveloped state of the art with regard to the pathogenesis of hepatitis C, one of skill in the art would have to start over at the beginning by envisioning a modification of the first combination of nucleic acid construct/delivery means/dose, or a completely new combination of nucleic acid construct/delivery means/dose and repeat the entire unpredictable process to identify

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a second combination of nucleic acid construct/delivery means/dose resulting in virus production upon transfection in vivo. Once again, the skilled artisan would have to then determine the toxic effects of the virus on the host animal. If the nucleic acid construct does not encode an attenuated virus with regard to the pathologies associated with HCV infection, which is likely given the lack of guidance in the prior art or specification as to how one would actually construct a nucleic acid encoding an attenuated HCV virus and given the underdeveloped state of the art with regard to the pathogenesis of hepatitis C, one of skill in the art would have to start over at the beginning and repeat the entire unpredictable process until a nucleic acid construct/delivery means/dose combination is identified that results in the production of an attenuated virus.

If finally successful in identifying a combination of nucleic acid construct/delivery means/dose effective in producing an attenuated virus upon transfection of target cells in vivo, one of skill in the art would have to determine whether the combination results in a protective immune response for animals not already exposed to the virus and in a therapeutic response for animals already infected with HCV. If unsuccessful in generating a protective or therapeutic immune response with the identified nucleic acid/delivery means/dose in the animal model, which is likely given that an effective vaccine against hepatitis C infection does not appear to have been disclosed in the prior art or instant specification, one of skill in the art would have to start at the beginning and repeat the entire, unpredictable process to identify a combination of nucleic acid construct/delivery means/dose that results in production of an attenuated virus and effective immune response upon transfection into the target cells of an animal.

Finally, if a combination of nucleic acid construct/delivery means/dose were identified in the model system (i.e. the chimpanzee), the combination would then have to be tested in humans.

It is noted that it is likely that a new means of delivery of the nucleic acid construct to target tissues will have to be developed because the only exemplified example in the specification and prior art appears to be direct injection of the nucleic acid encoding HCV into the liver. It is unlikely that this means of delivery is going to be acceptable for use in humans. Even aside from the probable necessity of developing an entirely new combination of nucleic acid construct/delivery means/dose for humans, it is unclear whether the results found in the chimpanzee model system for induction of an immune response by transfection with a nucleic acid encoding an attenuated virus will necessarily be predictive of success in humans. Therefore, practicing the claimed methods in humans with a nucleic acid construct found to produce an effective immune response in chimpanzees without pathological effects is unpredictable.

Given the extraordinary amount of unpredictable experimentation necessary to practice the claimed invention, it would require undue, unpredictable experimentation to practice the claimed methods of producing a therapeutic or protective immune response in animals by administration of a nucleic acid encoding an HCV. Therefore, the instant specification is not considered enabling for the rejected claims.

Response to Arguments

Applicant's arguments filed in Paper No. 8 have been fully considered but they are not persuasive. The response essentially argues: 1) the enablement rejection is rendered moot by the amendment of the claims to limit the scope of invention to embodiments encoding SEQ ID NO: 3, 2) the specification teaches how to make and use the specifically claimed embodiment, 3) post-filing references demonstrate that the claimed invention was enabled at the time of filing.

With regard to limiting the scope of the invention to embodiments featuring SEQ ID NO: 3 and the teachings of the specification with regard to making and using such constructs, the arguments are not persuasive on several grounds. Limiting the claimed invention to embodiments featuring SEQ ID NO: 3 does not address the issues raised by the examiner in making the rejection in Paper No. 6 and repeated above. The same problems apply. Moreover, the teachings specific to SEQ ID NO: 3 are merely prophetic in nature and do not make predictable the use of the claimed compositions and methods to provide protective immunity in humans.

With regard to the post-filing reference of Weiner et al (Exhibit 6), it is not clear from reading the reference that the vectors and methods described in the reference are taught explicitly in the instant specification. For example, Weiner et al use a construct featuring a specific combination of phage promoter and non-consensus or consensus sequences that do not appear to be specifically taught in the specification. Any differences between the teachings of Weiner et al and the instant specification must be considered as inventive experimentation considering the underdeveloped state and unpredictability of the art at the time of applicants' invention (see above). Therefore, Weiner et al cannot be considered as providing evidence that applicants' claimed invention was enabled at the time of invention.

With regard to the post-filing reference of Bukh et al, the reference is merely an abstract that discusses results with one monkey infected with a nondescribed vector in a nondescribed method, making it impossible to tell whether the methods and vectors used by Bukh et al involved inventive experimentation beyond the teachings of the instant specification at the time of filing. Both the Bukh et al and Weiner et al references are deficient with regard to providing

evidence that results seen in their experiments with the chimpanzee model are necessarily predictive of successful results in humans or that administration of the claimed compositions would not result in undesirable side-effects that would make an observed protective immunity moot. Even at this time, some 5 years post-filing for the instant application, the state of the art remains unpredictable. As indicated by Bukh et al, "Although it is well established that hepatitis C (HCV) infection is resolved in a subset of cases, the critical components of immunity to HCV have not been determined." (Exhibit 7, Paper No. 8). Thus, even if applicants were to demonstrate that the compositions and methods of Weiner et al or Bukh et al do not constitute inventive experimentation over the teachings of the instant specification, which has not been demonstrated to this point, the applicability of their teachings to the predictable and practical use of their methods in humans remains in doubt.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42-43, 45, 48, 51-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection, necessitated by applicants' amendment of the claims in Paper No. 8.**

Each of the rejected claims is vague and indefinite in that the metes and bounds of the phrase "...said nucleic acid encoding a human hepatitis C virus having the amino acid sequence of SEQ ID NO: 3..." are unclear. It is unclear how a viral particle which comprises elements obtained from a polypeptide comprising SEQ ID NO: 3 can itself comprise SEQ ID NO: 3.

Conclusion

No claims are allowed.

This application contains claims drawn to an invention nonelected with traverse in Paper No. 5. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the

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organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

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November 20, 2002

DAVID GUZO
PRIMARY EXAMINER
David Guzo